

CLAIM AMENDMENTS

1. (currently amended): A protein containing a modified human DDR2 cytosolic tyrosine kinase domain having an increased autophosphorylation and tyrosine kinase activity, wherein at least one of three tyrosines 736, 740 and 741 in the activation loop of the human DDR2 cytosolic tyrosine kinase domain having SEQ ID NO:1 is [[are]] modified by inducing ~~phosphorylations-~~ phosphorylation of said tyrosines, or by independently mutating at least one of said tyrosines to phenylalanine, alanine or glycine by [[a]] site-directed mutation.

2. (currently amended): The protein of claim 1, wherein tyrosine 740~~-in the activation loop of human DDR2 cytosolic tyrosine kinase domain~~ is essentially modified.

3. (currently amended): ~~The protein of claim 1~~ protein of claim 2, wherein tyrosine 740 ~~of the activation loop of the DDR2 cytosolic tyrosine kinase domain~~ is mutated to phenylalanine~~[[740]]~~.

4. (currently amended): A method for preparing a protein containing DDR2 cytosolic tyrosine kinase domain having increased autophosphorylation and tyrosine kinase activity, through phosphorylation of ~~tyrosines-~~ at least one tyrosine at the DDR2 cytosolic tyrosine kinase domain, comprising the following steps of:

- amplifying a DNA fragment which encodes an amino acid sequence sufficiently covering a DDR2 cytosolic tyrosine kinase domain protein, and introducing the amplified DNA fragment into a first viral expression vector to construct a recombinant viral expression vector for ~~DDR2 cytosolic tyrosine kinase domain-~~ said protein and generating a first recombinant virus carrying [[the]] said DDR2 cytosolic tyrosine kinase domain protein;

- amplifying a DNA fragment which encodes an amino acid sequence sufficiently covering a full-length c-Src or c-Src related protein, and introducing the amplified DNA fragment into ~~another separate-~~ a second virus expression vector ~~genome~~, to construct a second recombinant virus expression vector for ~~the c-Src or c-Src related-~~ said protein and generating recombinant virus carrying the c-Src or c-Src related protein;

- infecting ~~the obtained~~ first virus ~~carrying the DDR2 cytosolic tyrosine kinase domain and the obtained~~ and second virus ~~carrying the c-Src or c-Src related protein~~ into a host cell, co-expressing the proteins ~~together~~, and inducing [[a]] tyrosine phosphorylation at the DDR2 cytosolic tyrosine kinase domain by the tyrosine kinase activity of c-Src or c-Src related protein, to produce ~~a large amount of~~ a protein containing the DDR2 cytosolic tyrosine kinase domain with increased tyrosine phosphorylation;

- isolating and purifying ~~the obtained~~ said protein containing the DDR2 cytosolic tyrosine kinase domain with increased tyrosine phosphorylation.

5. (original): The method of claim 4, the c-Src related protein is selected from the group consisting of v-Src, Fyn, Yes, Lck, Hck, Lyn, Csk and Blk including their tyrosine kinase-activated versions.

6. (currently amended): The method of claim 4, wherein the DDR2 cytosolic tyrosine kinase domain protein is tagged with ~~one selected from the group consisting of glutathione-S-transferase, glutathione-S-transferase, thioredoxin or histidine oligomer.~~

7. (currently amended): The method of claim 4, wherein the first virus carrying the DDR2 cytosolic tyrosine kinase domain protein and the second virus carrying the c-Src or c-Src related protein are [[are]] simultaneously infected into the host cell at the ~~combination ratio~~ ratio of 1:3 to 3:1 and the MOI (multiplicity of infection) of 1 to 10.

8. (original): The method of claim 4, wherein the virus is a baculovirus and the host cell is an insect cell.

9. (currently amended): The method of claim 4, wherein the DDR2 cytosolic tyrosine kinase domain is human DDR2 cytosolic tyrosine kinase domain, and at least one of three tyrosines 736, 740 and 741 of human DDR2 cytosolic tyrosine kinase domain [[are]] having SEQ ID NO:1 is selectively phosphorylated.

10. (currently amended): The method of claim 9, wherein tyrosine 740 of human DDR2 cytosolic tyrosine kinase domain is essentially phosphorylated.

11. (currently amended): A method for preparing a protein containing a DDR2 cytosolic tyrosine kinase domain having an increased autophosphorylation and tyrosine kinase activity, by phosphorylating tyrosine at the DDR2 cytosolic tyrosine kinase domain protein, comprising the following steps of:

- amplifying a DNA fragment which encodes an amino acid sequence sufficiently covering a DDR2 cytosolic tyrosine kinase domain protein, and introducing the amplified DNA fragment into a viral expression vector to construct a recombinant viral expression vector for DDR2 cytosolic tyrosine kinase domain said protein and generating recombinant virus carrying the DDR2 cytosolic tyrosine kinase domain protein;

- ~~-- Infecting the obtained the virus of~~ infecting said virus carrying the DDR2 cytosolic tyrosine kinase domain into a host cell, to produce ~~a protein containing the DDR2 cytosolic tyrosine kinase domain, and then~~ said protein;

- treating the cells with H₂O₂ at the concentration of 10 μM to 1 mM to induce tyrosine phosphorylation at the ~~expressed~~ DDR2 cytosolic tyrosine kinase domain to obtain protein containing the DDR2 cytosolic tyrosine kinase domain with increased tyrosine phosphorylation; and

- isolating and purifying ~~the expressed~~ said protein containing the DDR2 cytosolic tyrosine kinase domain with ~~induced~~ increased tyrosine phosphorylation.

12. (currently amended): The method of claim 11, wherein the DDR2 cytosolic tyrosine kinase domain protein is tagged with ~~one selected from the group consisting of glutathione-S-transferase~~ glutathione-S-transferase, thioredoxin or histidine oligomer.

13. (currently amended): The method of claim 11, wherein the virus is a baculovirus and ~~the host~~ the host cell is an insect cell.

14. (currently amended): The method of claim 11, wherein the DDR2 cytosolic tyrosine kinase domain is human DDR2 cytosolic tyrosine kinase domain, and at least one of three

tyrosines 736, 740 and 741 of human DDR2 cytosolic tyrosine kinase domain ~~[[are]]~~ having SEQ ID NO:1 is selectively phosphorylated.

15. (currently amended): The method of claim 14, wherein tyrosine 740 ~~of human DDR2 cytosolic tyrosine kinase domain~~ is essentially phosphorylated.

16. (currently amended): A method for preparing a protein containing a DDR2 cytosolic tyrosine kinase domain having an increased autophosphorylation and tyrosine kinase activity, by mutating at least one of ~~tyrosines~~ tyrosine at the DDR2 cytosolic tyrosine kinase domain, comprising the following steps of:

- amplifying a DNA fragment which encodes an amino acid sequence sufficiently covering a mutant DDR2 cytosolic tyrosine kinase domain protein ~~[[where]]~~ wherein at least one of tyrosines at the DDR2 cytosolic tyrosine kinase domain ~~[[are]]~~ has been independently mutated to phenylalanine, alanine or glycine, by ~~[[a]]~~ site-directed mutagenesis; [[, and]]

- introducing the amplified DNA fragment into a viral expression vector to construct a recombinant viral expression vector for said mutant DDR2 cytosolic tyrosine kinase domain; ~~with mutation of at least one tyrosine to phenylalanine, alanine or glycine; and~~

- generating recombinant virus carrying ~~[[the]]~~ said mutant DDR2 cytosolic tyrosine kinase domain;

- infecting ~~the obtained said recombinant virus of the mutant DDR2 cytosolic tyrosine kinase domain~~ into a host cell, to produce ~~a protein containing~~ the mutant DDR2 cytosolic tyrosine kinase domain,

- isolating and purifying ~~the expressed said mutant DDR2 cytosolic tyrosine kinase domain protein containing the DDR2 cytosolic tyrosine kinase domain with mutation of at least one of tyrosines to phenylalanine, alanine or glycine.~~

17. (currently amended): The method of claim 16, wherein the DDR2 cytosolic tyrosine kinase domain protein is tagged with ~~one selected from the group consisting of glutathione-S-transferase, glutathione-S-transferase, thioredoxin or histidine oligomer.~~

18. (currently amended): The method of claim 16, wherein the virus is a baculovirus and ~~the host~~ the host cell is an insect cell.

19. (currently amended): The method of claim 16, wherein the DDR2 cytosolic tyrosine kinase domain is human DDR2 cytosolic tyrosine kinase domain, and at least one of three tyrosines 736, 740 and 741 of human DDR2 cytosolic tyrosine kinase domain ~~[[are]]~~ having SEQ ID NO:1 is independently mutated to phenylalanine, alanine or glycine.

20. (currently amended): The method of claim 14, wherein tyrosine 740 ~~of the DDR2 cytosolic tyrosine kinase domain~~ is ~~essentially~~ mutated to phenylalanine, alanine or glycine.

21. (currently amended): ~~A use of a protein containing a modified DDR2 cytosolic tyrosine kinase domain having an increased autophosphorylation and tyrosine kinase activity, to be utilized in developing medical drugs for treating. A method to identify a compound useful to treat a disease caused by an excessive autophosphorylation- autophosphorylation and tyrosine kinase activity of DDR2 protein, wherein at least one tyrosine of the activation loop of human DDR2 cytosolic tyrosine kinase domain are modified by inducing phosphorylations of tyrosines, or by independently mutating to phenylalanine, alanine or glycine by a site directed mutation which method comprises screening candidate compounds for interaction with the protein of claim 1.~~

22. (canceled)